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Age-related temporal and parietal cortical thinning in autism spectrum disorders

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Studies of head size and brain volume in autism spectrum disorders have suggested that early cortical overgrowth may be followed by prematurely arrested growth. However, the few investigations quantifying cortical thickness have yielded inconsistent results, probably due to variable ages and/or small sample sizes. We assessed differences in cortical thickness between high-functioning adolescent and young adult males with autism spectrum disorders ($n = 41$) and matched typically developing males ($n = 40$). We hypothesized thinner cortex, particularly in frontal, parietal and temporal regions, for individuals with autism spectrum disorders in comparison with typically developing controls. Furthermore, we expected to find an age × diagnosis interaction: with increasing age, more pronounced cortical thinning would be observed in autism spectrum disorders than typically developing participants. T_1-weighted magnetization prepared rapid gradient echo 3 T magnetic resonance imaging scans were acquired from high-functioning males with autism spectrum disorders and from typically developing males matched group-wise on age (range 12–24 years), intelligence quotient (≥85) and handedness. Both gyral-level and vertex-based analyses revealed significantly thinner cortex in the autism spectrum disorders group that was located predominantly in left temporal and parietal regions (i.e. the superior temporal sulcus, inferior temporal, postcentral/superior parietal and supramarginal gyri). These findings remained largely unchanged after controlling for intelligence quotient and after accounting for psychotropic medication usage and comorbid psychopathology. Furthermore, a significant age × diagnosis interaction was found in the left fusiform/inferior temporal cortex: participants with autism spectrum disorders had thinner cortex in this region with increasing age to a greater degree than did typically developing participants. Follow-up within group comparisons revealed significant age-related thinning in the autism spectrum disorders group but not in the typically developing group. Both thinner temporal and parietal cortices during adolescence and young adulthood and discrepantly accelerated age-related cortical thinning in autism spectrum disorders suggest that a second period of abnormal cortical growth (i.e. greater thinning) may be characteristic of these disorders.

Keywords: autism; brain; MRI; cortical thickness; age-related changes
Abbreviation: IQ = intelligence quotient

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Introduction

First described by Leo Kanner in 1943, autism is a disorder characterized by a triad of impairments, including social and communication difficulties and restricted interests/repetitive behaviour (APA, 2000). Strikingly prescient, Kanner noted in his original clinical description that 5 of the 11 cases had 'relatively large heads'. Subsequent work has confirmed this observation, as abnormally large brains (in at least a significant minority of cases) is one of the most consistent findings in the autism spectrum disorders literature. This finding is based on a variety of metrics, including measures of head circumference, post-mortem brain weight and brain volume from MRI (for review see Redcay and Courchesne, 2005). However, this effect appears to be age-dependent, as the most pronounced period of head/brain enlargement occurs in early postnatal periods, perhaps ages 1–4 years (Courchesne *et al.*, 2001; Hazlett *et al.*, 2005; Schumann *et al.*, 2010), while this atypical enlargement is increasingly absent later in development. For example, while post-mortem brain weights for children with autism spectrum disorders are generally comparable with those of same age controls, adults with autism spectrum disorders tend to have lighter post-mortem brains than adult controls (Bauman and Kemper, 1997). Furthermore, Aylward and colleagues (2002) found that children with autism spectrum disorders of 8–12 years of age had larger brain volumes than their same-age typically developing peers, while typically developing individuals and those with autism spectrum disorders ranging in age from 12 to 46 years had comparable brain volumes. Based on this and other evidence, Courchesne (2007) concluded in his review of the literature on early brain development in autism spectrum disorders that early cortical overgrowth is followed by prematurely arrested growth. Thus far, brain overgrowth in autism spectrum disorders appears to be due to increases in both grey and white matter (Courchesne *et al.*, 2001; Hazlett *et al.*, 2005). However, grey matter increases in autism spectrum disorders may be regionally specific with evidence of overgrowth present in frontal, temporal and parietal lobes, but a more typical growth pattern occurring in the occipital lobe (Palmen *et al.*, 2005). Whether or not the purported arrested growth of grey matter also occurs in a regionally specific manner remains largely unknown.

Recently, greater resolution in the measurement of grey matter has allowed a focus on cortical thickness, rather than grey matter volume, which represents the product of cortical thickness and surface area. Cortical thickness within neocortex primarily follows an inverted 'U' cubic pattern of development with an increase early in development followed by thinning in adolescence that is thought to reflect the sculpting forces of neuronal pruning (developmental trajectories for some phylogenetically older portions of cortex, however, are best explained by quadratic or linear functions; Shaw *et al.*, 2008).

The inverted U developmental trajectory of typical grey matter maturation poses a challenge for comparisons across cross-sectional studies as a developmental delay (or acceleration) in a given group could make cortical thickness relatively larger at one age but relatively smaller at a different age. This age effect, along with high individual variability (Lange *et al.*, 1997) and the difficulty of acquiring large sample sizes, has yielded a somewhat inconsistent picture in the few studies to date investigating cortical thickness in autism spectrum disorders. Among 8- to 12-year-old children, Hardan *et al.* (2006) found overall thicker cortex (particularly in the temporal lobe) for 17 relatively high-functioning males with autism spectrum disorders as compared with 14 typically developing males. However, it is important to note that the groups were not matched on intelligence quotient (IQ), with the autism spectrum disorders group scoring on average 20 points lower than the typically developing control group. In contrast, Chung *et al.* (2005) found mostly thinner cortex among 16 adolescent and young adult males (ages 12–25 years) with autism spectrum disorders versus 12 neurotypical control males. IQ levels were not reported in this study so it is unclear how well these groups were matched for intellectual ability, which may affect interpretation of these results as well. Hyde *et al.* (2009) documented a mixture of thicker (e.g. anterior and medial frontal regions, anterior cingulate, superior temporal sulcus, Heschl's gyrus and inferior parietal lobule) and thinner (e.g. portions of the pre-, para- and post-central gyri) cortex in 15 adolescent and adult males with high-functioning autism versus 15 neurotypical controls matched on age (ages 14–34 years) and IQ. Even more striking, Hadjikhani *et al.* (2006) found only thinner cortex among 14 adult males (mean age = 33 years) with high-functioning autism spectrum disorders versus 14 age- and IQ-matched control males, particularly in temporal, parietal and inferior frontal regions. Similarly, Wallace, Happé and Giedd (2009) found thinner temporal, parietal and frontal cortices for an adult male savant with Asperger's syndrome as compared to 14 male controls matched on age and verbal ability. Perhaps reconciling Hardan and colleagues' (2006) finding of increased cortical thickness in children with these findings of decreased cortical thickness in adolescents and adults, Hardan *et al.* (2009) completed a longitudinal paediatric study by collecting second scans (on average 1.9 years later) from many of the male participants with autism spectrum disorders in their 2006 study. They found accelerated thinning in the temporal and occipital lobes among children with autism spectrum disorders relative to typically developing children, although group differences dissipated after IQ covariation.

Taken together, the trend in findings from the autism spectrum disorders literature suggests that cortical thickness, like brain volumes, may follow a pattern in which early overgrowth is followed by prematurely arrested growth. However, the studies completed thus far have included <20 participants in each of the clinical and control groups, limiting statistical power. One recent exception to these patterns is a study of 76 individuals with autism spectrum disorders and 51 typically developing controls ranging in age from 10 to 60 years (Raznahan *et al.*, 2010). In this study, while temporal cortex thinned with increasing age in the typically developing group, there was little change in temporal cortical thickness in the autism spectrum disorders group. However, this study had several limitations worth noting. The very large age range studied includes periods of complex developmental cortical changes, which are curvilinear in nature; nevertheless, linear methods of analysis were used to model age effects. Furthermore, there are issues of matching and clinical characterization. Participants with autism spectrum disorders

were not matched to controls on IQ and just over 40% of the participants with autism spectrum disorders were not diagnosed using a gold-standard diagnostic tool. We therefore sought to improve upon this and other previous studies by concentrating on a more discrete period, adolescence and young adulthood, which is associated with a linear decline in cortical thickness, and by not only matching groups on IQ, but also acquiring detailed clinical characterization using gold-standard diagnostic instruments whenever possible. Although two studies (Chung *et al.*, 2005; Hyde *et al.*, 2009) evaluated cortical thickness in autism spectrum disorders during the adolescent and young adult age range, limited sample sizes (as in the Raznahan *et al.,* study that included 16 typically developing controls and 19 individuals with autism spectrum disorders who fell in the adolescent and young adult age range studied here) prevented examination of age effects within their samples. As adolescence and adulthood may be the period during which accelerated cortical thinning emerges in autism spectrum disorders, filling this gap in the literature is particularly important. Finally, as previously mentioned, matching on IQ in particular has been inconsistent in prior studies, limiting comparability across studies and interpretation, especially given the established effect of IQ on cortical thickness (Shaw *et al.*, 2006*a*; Narr *et al.*, 2007). Given findings of autism spectrum disorders-related thicker cortex during childhood and thinner cortex during adulthood, examination of cortical thickness in well-matched samples during the full range of adolescence and young adulthood may help to pinpoint the divergence of growth trajectories between individuals with autism spectrum disorders versus neurotypical controls.

Using high-resolution MRI, we sought to examine differences in cortical thickness between high-functioning adolescent and young adult males (mean age = 17 years) with autism spectrum disorders versus age- and IQ-matched typically developing males. We focused on male participants both to increase comparability with previous investigations of group differences of cortical thickness in autism spectrum disorders, which included only male participants, and to reflect the highly skewed sex ratio in autism spectrum disorders (at least 4 or 5:1 male-to-female ratio) that is particularly pronounced among higher functioning individuals (APA, 2000). Based on the trend in findings to date, we expect to document thinner cortex in autism spectrum disorders in the frontal, temporal and parietal lobes during this key transitional period of development. Complementing this approach, we investigated group differences in age-related cortical thickness changes, predicting a significant age × group interaction whereby more pronounced thinning in these brain regions would be observed in older participants with autism spectrum disorders relative to younger participants with autism spectrum disorders than would be seen when comparing older and younger typically developing participants.

Materials and methods

Participants

Participants were 40 typically developing males between 12 and 23 years of age and 41 high-functioning males with an autism spectrum disorder between 12 and 24 years of age, recruited from the Washington, DC, metropolitan area. All 41 participants with autism spectrum disorders met *Diagnostic and Statistical Manual-IV* diagnostic criteria as assessed by an experienced clinician (26 Asperger's syndrome, 11 high-functioning autism, three pervasive developmental disorder not otherwise specified and one with either Asperger's syndrome or high-functioning autism, which could not be distinguished because of missing early language-development data). Thirty-eight participants with autism spectrum disorders received the Autism Diagnostic Interview (ADI or ADI-R; Le Couteur *et al.*, 1989; Lord *et al*., 1994) and 40 participants with autism spectrum disorders received the Autism Diagnostic Observation Schedule (Lord *et al.*, 2000), administered by a trained, research-reliable clinician (38 participants with autism spectrum disorders received both the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule, and one received neither). Participants with autism spectrum disorders received either Module 3 ($n = 13$) or 4 ($n = 27$) of the Autism Diagnostic Observation Schedule. All scores from participants with autism spectrum disorders met cut-off for the category designated as 'Broad autism spectrum disorders' according to criteria established by the National Institute of Child Health and Human Development/National Institute on Deafness and Other Communication Disorders Collaborative Programs for Excellence in Autism (see Lainhart *et al.*, 2006). Exclusion criteria for the autism spectrum disorders group included an IQ of <70 or any known comorbid medical conditions, such as fragile X syndrome or other genetic disorders, and brain trauma/injury. In the autism spectrum disorders group, 22 individuals were taking one or more psychotropic medications: 12 were taking stimulants, 14 were taking selective serotonin reuptake inhibitors, four were taking atypical antipsychotics, two were taking anxiolytics, one was taking a mood stabilizer and one was taking a norepinephrine agonist.

Parents of typically developing children and the typically developing adults underwent telephone screenings. Typically developing individuals were excluded from participation if they had ever received mental health treatment for anxiety, depression or any other psychiatric condition, taken psychiatric medications, required special services in school, been diagnosed with a genetic disorder or neurological disorder or had brain trauma/injury that could potentially affect cognitive functioning and/or brain development. IQ scores were obtained from all participants. All full-scale IQ scores were ≥85 as measured by the Wechsler Abbreviated Scale of Intelligence (autism spectrum disorders: $n = 34$, typically developing: $n = 40$), Wechsler Adult Intelligence Scale-III (autism spectrum disorders: $n = 3$), Wechsler Intelligence Scale for Children-III (autism spectrum disorders: $n = 2$), or Wechsler Intelligence Scale for Children-IV (autism spectrum disorders: $n = 2$). Participant groups did not differ in terms of full-scale IQ, age or handedness (Table 1). Informed assent and consent were obtained from all participants and/or their parent/guardian when appropriate in accordance with a National Institutes of Health Institutional Review Board-approved protocol.

Imaging parameters

One high-resolution (1.07 × 1.07 × 1.2 mm) T_1-weighted structural image was obtained axially from each subject with a magnetization prepared rapid gradient echo sequence (124 slices, 1.2-mm slice thickness, 224 × 224 acquisition matrix, flip angle = 6°, field of view = 24 cm) on a 3 T General Electric Signa scanner (Milwaukee, Wisconsin) using an 8-channel head coil.

Table 1 Demographic characteristics

	Autism spectrum disorders ($n = 41$)	Typically developing ($n = 40$)
Age	16.75 (2.84) Range: 12.09–24.06	17.04 (2.73) Range: 12.42–23.77
FSIQ	113.27 (15.09) Range: 85–143	114.03 (10.74) Range: 97–136
VIQ	112.61 (17.23) Range: 77–153	112.96 (12.15) Range: 93–136
PIQ	111.02 (13.59) Range: 78–138	111.55 (11.15) Range: 91–142
Handedness (right:left)	37:4	36:4
ADI social[a]	18.71 (5.23) Range: 8–29	
ADI verbal communication[a]	15.00 (4.52) Range: 4–24	
ADI restricted and repetitive behaviour[a]	5.68 (2.89) Range: 0–12	
ADOS social[b]	8.38 (3.20) Range: 2–14	
ADOS communication[b]	4.15 (1.69) Range: 0–7	
ADOS stereotyped behaviour[b]	1.35 (1.56) Range: 0–6	

ADI = Autism Diagnostic Interview; ADOS = Autism Diagnostic Observation Schedule; FSIQ = full-scale intelligence quotient; PIQ = performance intelligence quotient; VIQ = verbal intelligence quotient. Data are mean (SD).
a $n = 38$.
b $n = 40$.

Surface reconstruction and cortical thickness calculation

The FreeSurfer image analysis suite was used to generate a cortical surface model providing a measure of cortical thickness at each surface vertex (Dale *et al.*, 1999, Fischl *et al.*, 1999, 2004; Fischl and Dale 2000). Initial steps in this surface-based, multi-step and semi-automated morphometric pipeline included visual inspection of data for motion artefacts, transformation to Talairach space, intensity normalization for correction of magnetic field inhomogeneities and removal of non-brain tissues (e.g. skull stripping). Cortical thickness representations were constructed using these procedures based on the entire 3D magnetic resonance volume. Cortical thickness was quantified at each surface location or vertex as the distance (in mm) from the grey/white boundary to the pial surface (Fischl and Dale, 2000). Spatial intensity gradients across tissue classes were used to create maps that are capable of detecting submillimetre differences between groups because they are not restricted to the voxel resolution of the original data. The resulting surface models generated were reviewed for accuracy and manually edited when needed. This method of cortical thickness measurement has been validated against post-mortem brains and histological analysis (Rosas *et al.*, 2002) and hand tracings (Kuperberg *et al.*, 2003; Salat *et al.*, 2004) and has shown good reliability across sites and platforms (Han *et al.*, 2006).

FreeSurfer, by relying on gyral and sulcal anatomy, enabled automatic parcellation of the cortical surface into 33 gyral regions per hemisphere, each of which had a mean cortical thickness value calculated (Fischl *et al.*, 2004; Desikan *et al.*, 2006). Neuroanatomical labels were provided at each vertex using the results of a manual training set, including probabilities of label-location concordance and spatial neighbourhood relationships, as well as local curvature information. In addition to the gyral-based cortical thickness measurements, vertex-level cortical thickness values were obtained and mapped onto a normalized cortical surface. These cortical thickness maps were smoothed with a 15 mm full width at half maximum kernel.

Statistical analysis

Group differences in gyral-level cortical thickness were assessed with a mixed-model Analysis of Variance (ANOVA) with diagnosis (autism spectrum disorders versus typically developing) as the between-subjects factor and both hemisphere (left versus right) and region (33 gyral regions) as the within-subjects factors. Follow-up one-way ANOVAs were used to examine group differences in gyral-level cortical thickness. Due to the relatively large number of follow-up one-way ANOVAs undertaken, a false discovery-rate correction (Benjamini and Hochberg, 1995) was performed per hemisphere to control for multiple comparisons. Additionally, the mixed-model ANOVA and follow-up one-way ANOVAs were re-run entering age and full-scale IQ as covariates, given prior age- and IQ-related findings in cortical thickness (Shaw *et al.*, 2006*a*, 2008).

In addition to this gyral-level analysis, group differences in cortical thickness were also examined on the surface maps vertex by vertex using a least squares general linear model. To control for multiple comparisons, cluster correction was completed using Monte Carlo simulation with 10 000 iterations (vertex-wise threshold of $P < 0.01$). This group comparison was run again entering full-scale IQ as a covariate to ensure that IQ variance did not contribute to any group differences.

In order to examine potentially discrepant age-related cortical thickness changes in the autism spectrum disorders versus typically developing groups, an age group (using a median split; $\leq$17 years versus $>$17 years) $\times$ diagnosis (autism spectrum disorders versus typically developing) interaction was run on the vertex-level data. Younger and older participants did not differ ($P > 0.05$) in terms of IQ (for both autism spectrum disorders and typically developing groups) or symptomatology scores (for the autism spectrum disorders group only). Pearson correlations between age and cortical thickness were run separately for the autism spectrum disorders and typically developing groups within significant clusters derived from testing the age group $\times$ diagnosis interaction. Two separate one-way follow-up analyses for each diagnostic group were run comparing vertex-level data for younger and older participants. Moreover, two additional one-way follow-up analyses were run comparing older autism spectrum disorders versus older typically developing individuals and younger autism spectrum disorders versus younger typically developing individuals. The same cluster correction procedure was applied to these analyses as well to control for multiple comparisons.

Results

When examining gyral-based differences in cortical thickness, we found a main effect of diagnosis [$F(1,79) = 4.70$, $P = 0.033$], a two-way interaction between group and region [$F(32,48) = 1.72$, $P = 0.044$], and a three-way interaction among group, region and hemisphere [$F(32,48) = 1.91$, $P = 0.021$]. Follow-up one-way ANOVAs revealed that several gyral-level brain regions, restricted primarily to left-sided temporal and parietal cortex, were significantly thinner in the autism spectrum disorders group than the typically developing group, after applying a false discovery rate correction (Table 2). No significant differences were detected in

Table 2 Gyral-based cortical thickness (mm) in individuals with autism spectrum disorders (n = 41) versus typically developing controls (n = 40)

Gyral region	Hemisphere	Autism spectrum disorders cortical thickness	Typically developing cortical thickness	F	P
Frontal lobe					
Superior frontal	L	2.94 (0.16)	2.99 (0.18)	1.70	0.196
	R	2.88 (0.14)	2.92 (0.20)	1.03	0.312
Caudal middle frontal	L	2.67 (0.16)	2.75 (0.18)	4.21	**0.043**
	R	2.63 (0.17)	2.65 (0.21)	0.24	0.626
Rostral middle frontal	L	2.59 (0.18)	2.64 (0.18)	1.75	0.190
	R	2.49 (0.16)	2.52 (0.18)	0.55	0.462
Pars opercularis	L	2.68 (0.16)	2.70 (0.18)	0.35	0.557
	R	2.49 (0.20)	2.58 (0.21)	3.97	0.050
Pars orbitalis	L	3.06 (0.22)	3.04 (0.23)	0.11	0.740
	R	2.99 (0.23)	2.98 (0.28)	0.01	0.935
Pars triangularis	L	2.73 (0.17)	2.79 (0.25)	1.77	0.188
	R	2.66 (0.17)	2.68 (0.22)	0.19	0.661
Lateral orbitofrontal	L	2.88 (0.20)	2.89 (0.19)	<0.01	0.956
	R	2.91 (0.18)	2.89 (0.21)	0.18	0.672
Medial orbitofrontal	L	2.74 (0.25)	2.73 (0.21)	0.01	0.913
	R	2.71 (0.28)	2.72 (0.23)	0.01	0.928
Precentral	L	2.61 (0.13)	2.66 (0.15)	1.93	0.168
	R	2.57 (0.13)	2.59 (0.16)	0.69	0.409
Paracentral	L	2.40 (0.21)	2.49 (0.20)	4.06	**0.047**
	R	2.41 (0.21)	2.50 (0.18)	3.75	0.057
Frontal pole	L	3.26 (0.33)	3.21 (0.32)	0.55	0.460
	R	3.12 (0.32)	3.23 (0.34)	2.04	0.158
Temporal lobe					
Superior temporal	L	2.78 (0.15)	2.87 (0.15)	5.96	**0.017**
	R	2.79 (0.18)	2.83 (0.17)	1.03	0.313
Middle temporal	L	2.99 (0.13)	3.05 (0.18)	2.77	0.100
	R	3.04 (0.16)	3.08 (0.17)	1.42	0.237
Inferior temporal	L	2.87 (0.21)	2.98 (0.15)	7.36	**0.008**[a]
	R	2.93 (0.19)	3.01 (0.17)	3.60	0.061
Entorhinal	L	3.08 (0.44)	3.34 (0.35)	8.89	**0.004**[a]
	R	3.04 (0.46)	3.16 (0.44)	1.64	0.204
Fusiform	L	2.56 (0.23)	2.71 (0.17)	8.85	**0.004**[a]
	R	2.63 (0.18)	2.69 (0.18)	2.20	0.142
Parahippocampal	L	2.61 (0.34)	2.65 (0.35)	0.26	0.610
	R	2.52 (0.38)	2.58 (0.27)	0.69	0.409
Temporal pole	L	3.30 (0.40)	3.30 (0.43)	0.01	0.921
	R	3.38 (0.46)	3.41 (0.43)	0.15	0.704
Transverse temporal	L	2.49 (0.23)	2.54 (0.22)	1.03	0.313
	R	2.55 (0.25)	2.58 (0.23)	0.27	0.603
Banks superior temporal sulcus	L	2.41 (0.16)	2.55 (0.24)	10.67	**0.002**[a]
	R	2.47 (0.21)	2.57 (0.20)	5.32	**0.025**
Parietal lobe					
Superior parietal	L	2.23 (0.16)	2.33 (0.14)	9.30	**0.003**[a]
	R	2.28 (0.13)	2.38 (0.15)	9.15	**0.003**[a]
Inferior parietal	L	2.49 (0.14)	2.61 (0.17)	10.88	**0.001**[a]
	R	2.59 (0.15)	2.69 (0.15)	10.24	**0.002**[a]
Supramarginal	L	2.56 (0.15)	2.65 (0.14)	8.95	**0.004**[a]
	R	2.66 (0.16)	2.67 (0.17)	0.11	0.745
Postcentral	L	2.08 (0.17)	2.18 (0.14)	8.03	**0.006**[a]
	R	2.08 (0.16)	2.14 (0.19)	2.62	0.109
Precuneus	L	2.30 (0.17)	2.37 (0.19)	3.33	0.072
	R	2.37 (0.15)	2.42 (0.17)	2.54	0.115
Occipital lobe					
Lateral occipital	L	2.26 (0.14)	2.31 (0.15)	2.93	0.091
	R	2.36 (0.13)	2.42 (0.14)	3.66	0.059
Lingual	L	2.14 (0.19)	2.14 (0.19)	<0.01	0.979
	R	2.18 (0.13)	2.20 (0.12)	0.37	0.545
Cuneus	L	1.95 (0.19)	1.96 (0.18)	0.07	0.799
	R	2.02 (0.18)	2.01 (0.17)	0.08	0.781
Pericalcarine	L	1.80 (0.21)	1.72 (0.14)	3.65	0.060
	R	1.76 (0.18)	1.75 (0.14)	0.14	0.708
Cingulate					
Rostral anterior cingulate	L	2.59 (0.31)	2.60 (0.24)	0.03	0.869
	R	2.50 (0.39)	2.57 (0.23)	0.83	0.365
Caudal anterior cingulate	L	2.24 (0.29)	2.26 (0.26)	0.10	0.750
	R	2.23 (0.30)	2.26 (0.24)	0.34	0.559
Posterior cingulate	L	2.43 (0.20)	2.46 (0.17)	0.50	0.483
	R	2.42 (0.22)	2.43 (0.18)	0.11	0.746
Isthmus cingulate	L	2.51 (0.22)	2.60 (0.19)	3.08	0.083
	R	2.52 (0.20)	2.58 (0.16)	2.29	0.134

Bold values indicates $P < 0.05$; L = left; R = right. Data are mean (SD).
a Survived false discovery rate correction ($q < 0.05$).

regions outside of the temporal or parietal lobes, and no brain regions were significantly thicker in the autism spectrum disorders group as compared with the typically developing group. Adding age and/or full-scale IQ as a covariate to the mixed-model omnibus ANOVA and to the follow-up one-way ANOVAs did not change the gyral-level results (all P's remained <0.05). Diminished cortical thickness in autism spectrum disorders was not the result of tissue compartment (i.e. grey matter to white matter) substitution, as white matter volumes were either not different between the groups or significantly smaller (P's < 0.05) in the autism spectrum disorders group.

Vertex-by-vertex analyses conducted on the cortical surface yielded similar results to the gyral-level analyses. As illustrated in Fig. 1, thinner cortex was found in the autism spectrum disorders group, localized to temporal and parietal regions, most prominently in the left hemisphere. Adding full-scale IQ as a covariate did not alter these findings.

Psychotropic medication usage and comorbidity

To evaluate the effect of psychotropic medication, the gyral and vertex-based analyses were re-run comparing cortical thickness between the full typically developing group (n = 40) and participants with autism spectrum disorders who were not taking psychotropic medications at the time of their visit (n = 16). The pattern of results (Supplementary Fig. 1) remained the same with thinner cortex in primarily left-sided temporal and parietal regions in the autism spectrum disorders group when compared with the typically developing group (P's < 0.05). Similarly, 33 of the 41 participants with autism spectrum disorders were administered the Child Behaviour Checklist, a reliable and well-validated

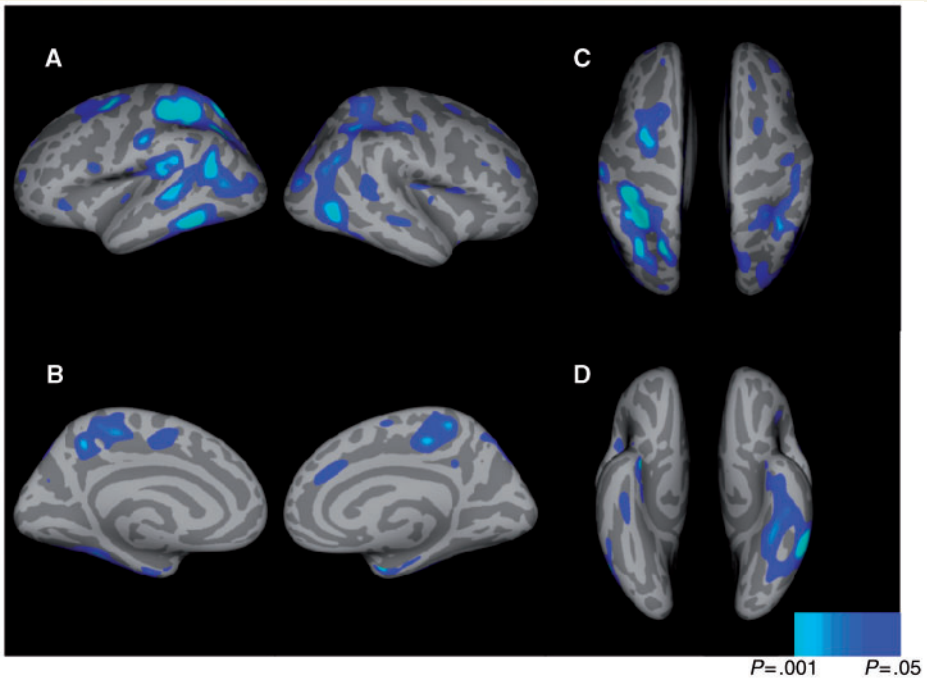

Figure 1 Inflated surface maps (dark grey = sulci; light grey = gyri) of thinner cortex in males with autism spectrum disorders versus typically developing males in the **A** lateral, **B** medial, **C** dorsal and **D** ventral views. Areas in light blue survived cluster correction (all P's < 0.003).

parent rating of psychopathology in 6- to 18-year-old children and adolescents. T-scores (mean = 50, SD = 10) can be derived from Diagnostic and Statistical Manual-oriented scales classified into affective, anxiety, attention-deficit/hyperactivity, conduct, oppositional and somatic problems (Achenbach *et al.*, 2003). Notably, scores are highly skewed (with the lowest T-score = 50) because these scales are designed to assess psychopathology, not normal variation in these behaviours. Using these scores, subgroups can be derived based on whether or not an individual exhibits clinically elevated (T-scores of $\geq$65) symptoms on one or more of these Diagnostic and Statistical Manual-oriented scales. Sufficiently sized subgroups for further cortical thickness analysis ($n = 11$–13) were obtained for three (affective, anxiety, attention-deficit/hyperactivity) of the six behavioural domains ($n < 5$ for the other three scales), consistent with prior studies examining comorbid psychopathology in autism spectrum disorders (e.g. Leyfer *et al.*, 2006). When comparing individuals with autism spectrum disorders with elevated Child Behaviour Checklist scores in these three domains against the full typically developing group, results remained similar to those presented in Table 2 and Fig. 1. Similarly, comparing cortical thickness in individuals with autism spectrum disorders with elevated Child Behaviour Checklist scores versus those individuals with autism spectrum disorders without elevated scores resulted in no significant differences.

Age group × diagnosis interaction

Although age as a covariate had no demonstrable effect on group differences in cortical thickness at the gyral-level, age effects may not conform to gyral-based neuroanatomy so that higher spatial resolution is required. Indeed, in vertex-based analyses, the age group × diagnosis interaction was significant after cluster correction ($P = 0.05$) primarily in the vicinity of the left inferior temporal and left fusiform gyri (see Fig. 2A for a map of this region and Fig. 2B for a histogram depicting the interaction). Moreover, the correlation between age and cortical thickness in this region was significant for autism spectrum disorders ($r = -0.48$, $P = 0.002$), but not typically developing ($r = -0.09$, $P = 0.59$) individuals (see Fig. 2C for a scatterplot of these correlations). A follow-up one-way comparison revealed that left fusiform/inferior temporal gyri along with the left orbitofrontal cortex, right pars triangularis and bilateral superior (and to a lesser extent lateral) frontal cortices were thinner in individuals with autism spectrum disorders >17 years of age versus younger (12- to 17-year-old) children with autism spectrum disorders (P's < 0.04, cluster corrected; see Fig. 3). Only one region, the right temporal pole, was found to be thicker in the older autism spectrum disorders group versus the younger autism spectrum disorders group ($P = 0.03$, cluster corrected). This pattern of results was not observed in the typically developing individuals, who displayed more modest, non-significant thinning in the older age group. Complementing these findings, in the one-way follow-up comparison of older individuals with autism spectrum disorders versus older typically developing individuals, thinner cortex in individuals with autism spectrum disorders was found in the vicinity of the left fusiform/inferior temporal gyri ($P = 0.0001$, cluster corrected). For the comparison of younger individuals with autism spectrum disorders versus younger typically developing individuals, thinner cortex in individuals with autism spectrum disorders was limited primarily to the parietal cortex bilaterally (P's < 0.05, cluster corrected; see Fig. 4).

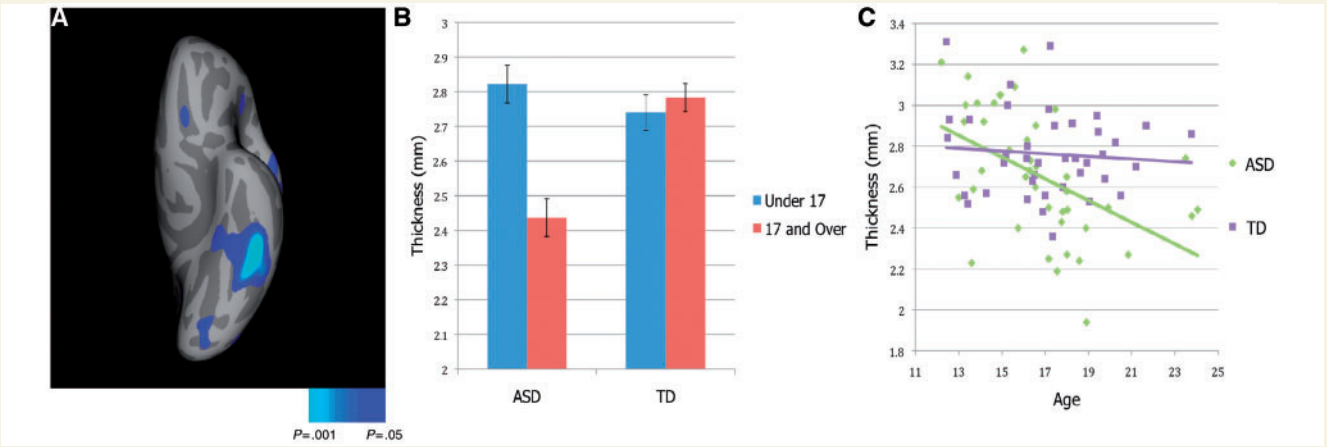

Figure 2 (**A**) Left hemisphere ventral view of an inflated surface map (dark grey = sulci; light grey = gyri) of the significant interaction between age group and diagnostic group. Blue indicates discrepantly thinner cortex with increasing age in males with autism spectrum disorders versus typically developing males. The area in light blue survived cluster correction. (**B**) Histogram of the age group by diagnosis interaction in left inferior temporal/fusiform gyri (area depicted in light blue in Fig. 2A). (**C**) Scatterplot of the age group × diagnosis interaction (autism spectrum disorders group $R^2 = 0.23$; typically developing group $R^2 = 0.01$) in left inferior temporal/fusiform gyri (area depicted in light blue in Fig. 2A). ASD = autism spectrum disorders; TD = typically developing.

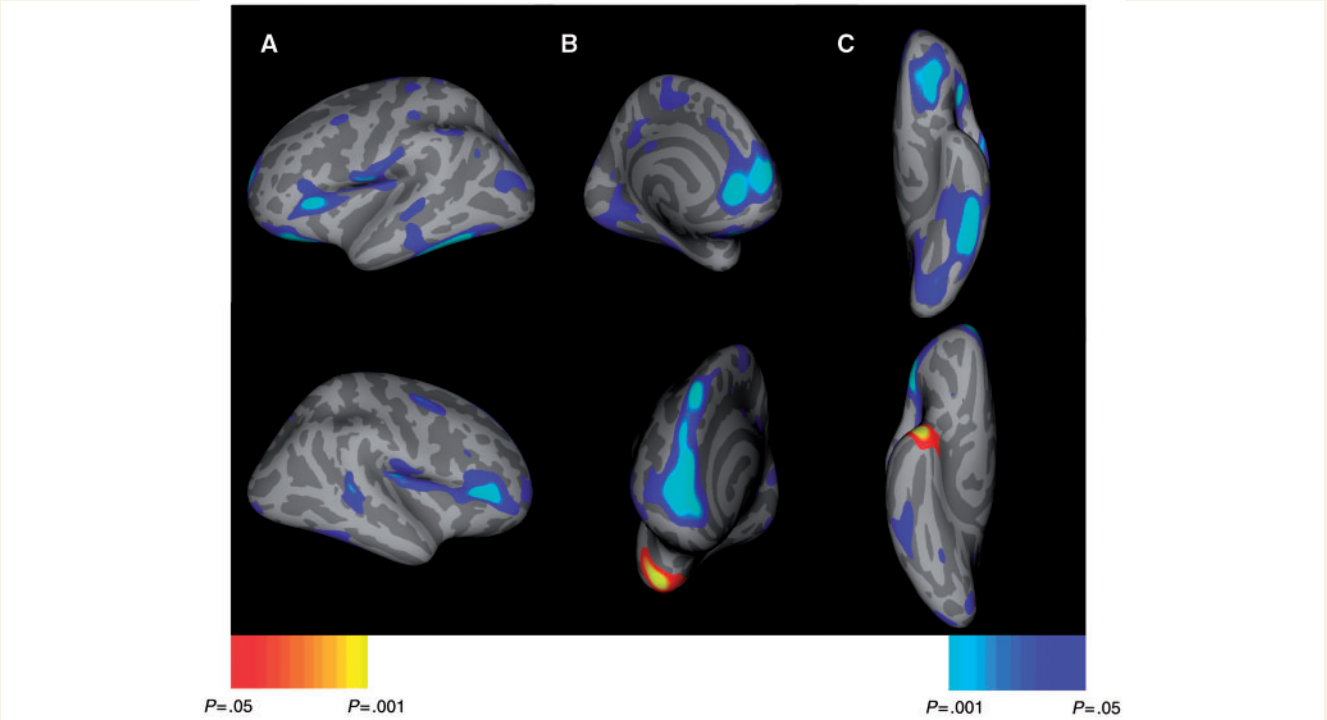

Figure 3 Findings of predominantly thinner (in blue) cortex for individuals with autism spectrum disorders >17 years of age versus those ≤17 years in the (**A**) left and right lateral, (**B**) left and right medial and (**C**) left and right ventral views. Areas in light blue and yellow survived cluster correction.

Discussion

Consistent with our predictions, we found thinner cortex predominantly in left temporal and parietal cortices in high functioning adolescent and young adult males (ages 12–24 years) with autism spectrum disorders relative to a well-matched group of typically developing males. We also found evidence for group differences between the autism spectrum disorders and typically developing groups in age-related cortical thickness changes. Individuals with autism spectrum disorders >17 years of age, relative to individuals with autism spectrum disorders ≤17 years, had robustly thinner (particularly temporal) cortex, while such age-related patterns in

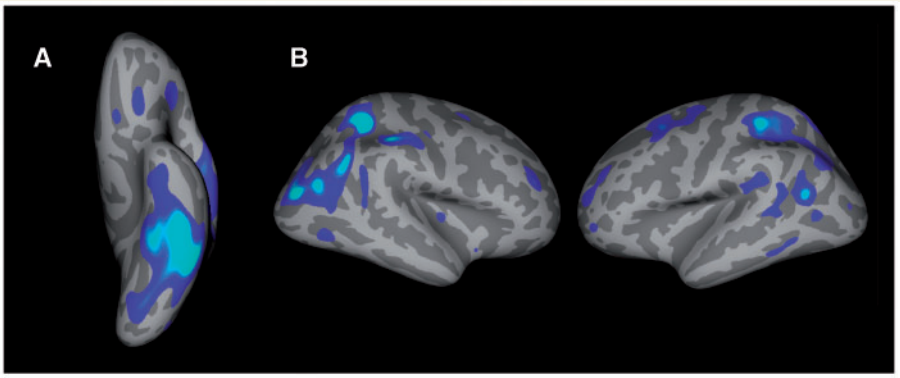

Figure 4 Areas of significantly thinner cortex for individuals with autism spectrum disorders versus typically developing controls (**A**) >17-years old (left hemisphere ventral view) and (**B**) ≤17 years (right and left hemisphere lateral views). Areas in light blue survived cluster correction (all P's < 0.04).

the typically developing group were less pronounced. Our study, by focusing on the relatively understudied period of adolescence and young adulthood, adds to a growing body of work on developmental trajectories in autism spectrum disorders. Specifically, our findings suggest that, in addition to the well-documented early brain overgrowth in autism spectrum disorders, there is probably prematurely arrested growth during the late childhood/early adolescent age range, followed by accelerated regionally specific thinning during adolescence and young adulthood.

More specifically, the present results complement earlier findings of thinner cortex in adults with autism spectrum disorders (Chung *et al.*, 2005; Hadjikhani *et al.*, 2006; Wallace *et al.*, 2009) and may therefore pinpoint adolescence as the time window during which the cortical growth trajectories diverge a second time (in addition to the overgrowth during early development). Taken from this perspective, these findings somewhat parallel those previously reported for amygdala volumes; the amygdala was found to be significantly larger among pre-adolescent children (ages 7.5–12.5 years) with autism spectrum disorders versus typically developing children in this age range, while similar amygdala volumes were reported for adolescents (ages 12.75–18.5 years) with autism spectrum disorders versus their same age typically developing peers (Schumann *et al.*, 2006). Placed in the context of the wider literature, the current findings suggest that the presence of thinner cortex continues into young adulthood, although it is unclear whether the cortical developmental trajectory in autism spectrum disorders across childhood, adolescence and young adulthood is parallel to that found in typical development. Longitudinal studies are needed to validate this proposed accelerated cortical thinning during adolescence and young adulthood in autism spectrum disorders.

The regional specificity of the present findings was largely consistent with prior studies (that have documented both thinner and thicker cortex in autism spectrum disorders depending on the age group studied). As in the present study, thinner temporal and parietal cortices, particularly in the left hemisphere, were also documented by Hadjikhani *et al.* (2006) and Wallace *et al.* (2009) among high-functioning adult males on the autism spectrum. Hardan *et al.* (2006) measured cortical thickness over lobar regions, finding that thicker cortex in autism spectrum disorders was restricted to temporal and parietal cortices during childhood, just as thinner cortex was confined to those regions in our sample of adolescent and young adult males with autism spectrum disorders. Similarly, the more pronounced age-related cortical thinning in autism spectrum disorders documented in the current study was confined to the temporal cortex, corresponding to Hardan *et al.*'s (2009) longitudinal study finding accelerated thinning in the temporal cortex in the autism spectrum disorders group. In the context of a large cross-sectional study (autism spectrum disorders $n = 76$), Raznahan *et al.* (2010) also found significant age × diagnosis interactions, primarily in the temporal cortex. However, the pattern of group differences was discrepant from those shown here. While we found more pronounced cortical thinning in individuals with autism spectrum disorders than in typically developing individuals, Raznahan *et al.* found relatively flat age-related changes in the temporal cortex in the autism spectrum disorders group, unlike the typically developing group, which displayed thinner temporal cortex with increasing age. The different age ranges studied and the modelling chosen in that study very likely contributed to inconsistent findings. While our study concentrated on adolescence and young adulthood (associated with a linear decline in cortical thickness), their study encompassed a much larger age band, with individuals ranging in age from 10 to 60 years (periods of both decline and levelling off of cortical thickness developmental curves, suggesting that their use of linear models may be problematic). Additionally, their findings do not fit the general pattern in the literature of increased cortical thinning in autism spectrum disorders at later ages. Finally, participants with autism spectrum disorders in their study, as in most other studies of cortical thickness in autism spectrum disorders, were not matched to the control group on IQ. Instead, any IQ effects were accounted for via covariation only.

Coupled with findings of early overgrowth, the increasingly thinner cortex during adolescence and young adulthood could reflect a leftward shift in autism spectrum disorders of the inverted U-shaped pattern of grey matter observed for both volumes and cortical thickness during typical development (Giedd *et al.*,

1999; Shaw *et al.*, 2008), perhaps reflecting synaptogenesis/neurogenesis gone awry. It could be that, in autism spectrum disorders, early cortical overgrowth is followed by either earlier synaptic pruning or over-pruning during adolescence, a period characterized by selective synaptic elimination and arborization of dendrites and axons (Huttenlocher and Dabholkar, 1997). We are reassured that findings reported in the present study do not simply reflect tissue compartmental shift (i.e. as grey matter decreases, white matter increases), given that white matter volume in our sample is either not different between groups or indeed smaller in the autism spectrum disorders group. Similarly, whether or not a participant with autism spectrum disorders was taking psychotropic medication or exhibited clinically elevated psychopathology did not change the pattern of results. This rules out medication usage and comorbid psychopathology as contributory factors to our findings of cortical thinning, and furthermore, suggests that the cortical thinning documented here is a result of autism spectrum disorders, not comorbid conditions. What genetic and/or environmental forces contribute to this abnormal cortical growth trajectory remain unknown, although it is well established that brain volumes (Wallace *et al.*, 2006), and to a lesser extent cortical thickness (Lenroot *et al.*, 2009), during childhood and adolescence are highly heritable. Recently, Wassink and colleagues (2007) linked cortical grey matter overgrowth in autism spectrum disorders with variation of the serotonin transporter gene, though Raznahan and colleagues (2009) could not replicate this result. Davis *et al.* (2008) also linked cortical enlargement in autism spectrum disorders with the 'low activity' allele of the Monoamine oxidase A (MAOA) gene. The cortical growth trajectory in autism spectrum disorders may also vary for individuals with optimal versus more typical outcomes, as has been shown in attention-deficit/hyperactivity disorder (Shaw *et al.*, 2006*b*). Future research should continue to explore links between genetic/environmental factors and this atypical trajectory of brain growth, particularly focusing on cortical thinning, in autism spectrum disorders.

Although these results are promising, there are limitations to consider. First, the present study included only high-functioning males; therefore, this pattern of findings may not apply to either lower functioning individuals or females with autism spectrum disorders. This study focused on high-functioning individuals with autism spectrum disorders in order to better isolate autism spectrum disorders-specific effects on cortical thickness, above and beyond intellectual disability and because prior studies demonstrated significant associations between IQ and cortical thickness (Shaw *et al.*, 2006a; Narr *et al.*, 2007). Additionally, the sample was restricted to males, because previous work reveals sex differences in neuroanatomy, not only in typical development (Lenroot *et al.*, 2007), but also in autism spectrum disorders (Bloss and Courchesne, 2007; Craig *et al.*, 2007; Schumann *et al.*, 2010). Finally, this investigation was cross-sectional in design, though larger than previously reported similar studies. Longitudinal designs, such as those conducted by Schumann *et al.* (2010) in early development and Hardan *et al.* (2009) in late childhood, are needed in later developmental windows to more definitively test postulations surrounding the cortical growth trajectory in autism spectrum disorders.

Much has been made of the unique and atypical early brain overgrowth in autism spectrum disorders, perhaps to the relative detriment of later developmental changes in this group. In order to fully understand the pattern of neural growth and development in autism spectrum disorders, a snapshot of various developmental windows is required, as we have done here for the period of adolescence and young adulthood. Once this pattern of atypical development has been established via cross-sectional and longitudinal studies, we can begin to investigate genetic and environmental mechanisms as well as intervention effects on this trajectory.

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Supplementary material

Supplementary material is available at *Brain* online.

References

Achenbach TM, Dumenci L, Rescorla LA. DSM-oriented and empirically based approaches to constructing scales from the same item pools. J Clin Child Adolesc Psychol 2003; 32: 328–40.

American Psychiatric Association. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR). 2000. Washington, DC.

Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. Neurology 2002; 59: 175–83.

Bauman ML, Filipek PA, Kemper TL. Early infantile autism. Int Rev Neurobiol 1997; 41: 367–86.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc 1995; 57: 289–300.

Bloss CS, Courchesne E. MRI neuroanatomy in young girls with autism: a preliminary study. J Am Acad Child Adolesc Psychiatry 2007; 46: 515–23.

Chung MK, Robbins SM, Dalton KM, Davidson RJ, Alexander AL, Evans AC. Cortical thickness analysis in autism with heat kernel smoothing. Neuroimage 2005; 25: 1256–65.

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology 2001; 57: 245–54.

Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, et al. Mapping early brain development in autism. Neuron 2007; 56: 399–413.

Craig MC, Zaman SH, Daly EM, Cutter WJ, Robertson DM, Hallahan B, et al. Women with autistic-spectrum disorder: magnetic resonance imaging study of brain anatomy. Br J Psychiatry 2007; 191: 224–8.

Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis - I. Segmentation and surface reconstruction. Neuroimage 1999; 9: 179–94.

Davis LK, Hazlett HC, Librant AL, Nopoulos P, Sheffield VC, Piven J, et al. Cortical enlargement in autism is associated with a functional VNTR in the monoamine oxidase A gene. Am J Med Genet B Neuropsychiatr Genet 2008; 147B: 1145–51.

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006; 31: 968–80.

Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 2000; 97: 11050–5.

Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis - II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 1999; 9: 195–207.

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex 2004; 14: 11–22.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 1999; 2: 861–3.

Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H. Anatomical differences in the mirror neuron system and social cognition network in autism. Cereb Cortex 2006; 16: 1276–82.

Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, et al. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 2006; 32: 180–94.

Hardan AY, Libove RA, Keshavan MS, Melhem NM, Minshew NJ. A preliminary longitudinal magnetic resonance imaging study of brain volume and cortical thickness in autism. Biol Psychiatry 2009; 66: 320–6.

Hardan AY, Muddasani S, Vemulapalli M, Keshavan MS, Minshew NJ. An MRI study of increased cortical thickness in autism. Am J Psychiatry 2006; 163: 1290–2.

Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, et al. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Arch Gen Psychiatry 2005; 62: 1366–76.

Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997; 387: 167–78.

Hyde KL, Samson F, Evans AC, Mottron L. Neuroanotomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. Hum Brain Mapp 2009; 31: 556–66.

Kanner L. Autistic disturbances of affective contact. Nerv Child 1943; 2: 217–50.

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 2003; 60: 878–88.

Lainhart JE, Bigler ED, Bocian M, Coon H, Dinh E, Dawson G, et al. Head circumference and height in autism: A study by the Collaborative Program of Excellence in Autism. Am J Med Genet A 2006; 140A: 2257–74.

Lange N, Giedd JN, Castellanos FX, Vaituzis AC, Rapoport JL. Variability of human brain structure size: ages 4-20 years. Psychiatry Res 1997; 74: 1–12.

Le Couteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, et al. Autism Diagnostic Interview - a standardized investigator-based instrument. J Autism Dev Disord 1989; 19: 363–87.

Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 2007; 36: 1065–73.

Lenroot RK, Schmitt JE, Ordaz SJ, Wallace GL, Neale MC, Lerch JP, et al. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. Hum Brain Mapp 2009; 30: 163–74.

Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, et al. Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. J Autism Dev Disord 2006; 36: 849–61.

Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 2000; 30: 205–23.

Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised - a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 1994; 24: 659–85.

Narr KL, Woods RP, Thompson PM, Szeszko P, Robinson D, Dimtcheva T, et al. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cereb Cortex 2007; 17: 2163–71.

Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lahuis BE, et al. Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychol Med 2005; 35: 561–70.

Raznahan A, Pugliese L, Barker GJ, Daly E, Powell J, Bolton PF, et al. Serotonin transporter genotype and neuroanatomy in autism spectrum disorders. Psychiatr Genet 2009; 19: 147–50.

Raznahan A, Toro R, Daly E, Robertson D, Murphy C, Deeley Q, et al. Cortical anatomy in autism spectrum disorder: an in vivo mri study on the effect of age. Cereb Cortex 2010; 20: 1332–40.

Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports. Biol Psychiatry 2005; 58: 1–9.

Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 2002; 58: 695–701.

Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RSR, Busa E, et al. Thinning of the cerebral cortex in aging. Cereb Cortex 2004; 14: 721–30.

Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, et al. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. J Neurosci 2010; 30: 4419–27.

Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH, et al. The amygdala is enlarged in children but not adolescents with autism; The hippocampus is enlarged at all ages. J Neurosci 2004; 24: 6392–401.

Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, et al. Intellectual ability and cortical development in children and adolescents. Nature 2006a; 440: 676–9.

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, et al. Neurodevelopmental trajectories of the human cerebral cortex. J Neurosci 2008; 28: 3586–94.

Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, et al. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2006b; 63: 540–9.

Wallace GL, Happe F, Giedd JN. A case study of a multiply talented savant with an autism spectrum disorder: neuropsychological functioning and brain morphometry. Philos Trans R Soc Lond B Biol Sci 2009; 364: 1425–32.

Wallace GL, Schmitt JE, Lenroot R, Viding E, Ordaz S, Rosenthal MA, et al. A pediatric twin study of brain morphometry. J Child Psychol Psychiatry 2006; 47: 987–93.

Wassink TH, Hazlett HC, Epping EA, Arndt S, Dager SR, Schellenberg GD, et al. Cerebral cortical gray matter overgrowth and functional variation of the serotonin transporter gene in autism. Arch Gen Psychiatry 2007; 64: 709–17.